UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Date: June 18, 2019

Subject: **Zeta-Cypermethrin.** Review of "Dislodgeable Residue Study for Y-TEX Dog Tag Medallion for Registration Review."

PC Code: 129064
Decision No.: 544188
Petition No.: NA
Risk Assessment Type: Study Review
T**XR No.:** NA
MRID No.: 50675201

DP Barcode: D448836
EPA Reg. Number: 39039-14
Regulatory Action: Registration Review
Case No.: 2130
CAS No.: 97955-44-7
40 CFR: §180.418

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Introduction

The Pesticide Re-evaluation Division (PRD) requested that HED review a study entitled "Dislodgeable Residue Study for Y-TEX Dog Tag Medallion" in response to comments received on the registration review Draft Risk Assessment for the pyrethroid insecticide zeta-cypermethrin.

Executive Summary

As described in the recent 2016 tetrachlorvinphos (TCVP) risk assessment (W. Britton, D436833, 12/21/2016), due to the uncertainty associated with whether pet collars are liquid and/or dust formulated products, residential handler exposures for pet collar applications are assessed assuming pet collars could be liquid and solid (dust) formulations concurrently, with varying ratios of liquid/dust (e.g., 99/1, 50/50, and 1/99 liquid/dust). If registrants wish to refine the exposure and risk estimates associated with pet collars, they can submit a "torsion" study which characterizes the liquid vs. dust ratio, and/or they could submit a "dislodgeable fur" residue, to determine how much of residue is available for transfer when adults or children interact with treated pets.

The Health Effects Division (HED) conducted a draft risk assessment (DRA) for the insecticide, zeta-cypermethrin (D425964; M. Collantes; 12/21/2017). Since the pet collar medallion product is similar in composition to a pet collar, HED assessed risks from exposure to the pet collar medallion using the same liquid and solid ratio approach as used for pet collar assessments. Using this approach, risk estimates of concern were identified for the following residential scenario:

- Residential post-application exposure from zeta-cypermethrin, combined dermal and incidental oral exposures for children 1 to <2 years old from contact with pets treated with pet collar medallion. A quantitative residential post-application assessment resulted in margins of exposures (MOEs) ranging from 1.9 to 190 with a level of concern (LOC) of 300 for children 1 to < 2 years old.

Y-TEX Corporation responded to the Agency's assessment in commenting that HED's residential zeta-cypermethrin post-application risk estimate for the YT-1601 Dog Tag/Medallion [EPA Reg. No. 39039-14] is based on the assumption that the entire dose of the active ingredient is immediately released onto the hair coat of the animal (as in a spot-on treatment). In support of their comments, Y-TEX Corporation submitted dislodgeable (herein referred to as "transferable") residue and release rate study data (MRID 50675201) to the EPA. Using the EPA's treated pet dermal exposure calculator (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residentialpesticide) with the same toxicity and exposure inputs, Y-TEX Corporation submitted an assessment of residential post-application exposure and risk. Y-Tex Corporation's risk assessment states that their end-use product is not a dust formulation, and therefore a torsion study is not necessary to support their product's registration (i.e., all MOEs assuming the medallion is a liquid formulation are greater than the LOC).

HED has reviewed the transferable residue data provided by Y-TEX Corporation. An ethics review was also performed and HED determined the data to be acceptable for risk quantitation (D436833, M. Arling, 4/30/2019) and refinement of the residential post-application exposure estimates. HED will continue to rely on its existing approach for incorporating chemical-specific transferable residue data in the zeta cypermethrin exposure and risk assessment. HED will also continue to rely on its current approach of assessing the medallion both as a liquid and a solid (99/1, 50/50, and 1/99 liquid/dust). In the absence of submitted data or comments regarding the residues released from the medallion (i.e., liquid vs. dust), HED will also continue to recommend

submission of a mechanical dust torsion study to provide clarity on the residues potentially released from the medallion.

Use Profile

The YT-1601 Dog Tag, EPA Reg. No. 39039-14, is formulated as a medallion worn around a dog's neck containing 10% active ingredient (a.i.). The medallion varies in size from 4 grams to 8 grams and is clasped onto the dog collar.

Hazard Characterization/Endpoints and Uncertainty Factors

The toxicological database is considered complete for risk assessment purposes. A detailed discussion of the toxicology studies and the effects observed across the database is included in the 2017 Draft Human Health Risk Assessment for Registration Review (D425964, M. Collantes 12/21/2017).

Summary of Dislodgeable Residue Study for YT-1601 Dog Tag Registration Number 39039-14 (MRID 50675201)

Y-TEX Corporation conducted a transferable residue study using the dog tag/medallion end-use product (Reg. No. 39039-14); the study was conducted in association with an efficacy study for the product. Dislodgeable residues were collected by the study author wearing cotton gloves while performing a full body examination of a dog wearing a four-gram medallion; the examination was conducted 3-days post-application to evaluate product efficacy for tick control. Results indicated a maximum glove residue value of 0.8 mg of zeta-cypermethrin three days post-application. These results were further supported by measurable zeta-cypermethrin in hair/fur samples taken just before examination on day 23 (the only day residues in hair/fur were detectable). at a maximum of 0.062 mg/g of hair. The registrant submission presented estimated risks using the following: EPA's treated pet dermal exposure calculator (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide); the same toxicity inputs as EPA; three times the maximum value in the transferable residue study (2.4 mg Zeta-cypermethrin); and assuming the product is released either entirely in the liquid form (100% liquid) or the solid form (100%) solid. The estimated post-application risks, which are not of concern, are presented below in Figure 1.

Figure 1. Registrant Estimated Child Post-Application Exposures Assuming 100% Liquid and 100% Solid Formulation Release for All Size Dog Tags (Small, Medium, and Large)

Lifestage	Pet Size	AR (mg ai)	Absorbed Dose (mg/kg/day)	MOE (rounded)
		100% Liquid		
Child	Small	2.4	0.00	26,000
	Medium	3.6	0.00	41,000
	Large	4.8	0.00	48,000
		100% Solid		
Child	Small	2.4	0.02	970
	Medium	3.6	0.01	1500
	Large	4.8	0.01	1800

HED Updated Residential Post-Application Exposures and Risks

HED has updated the residential post-application risk estimates associated with exposure to the pet medallion using the submitted residue transfer study data and assuming the medallion could be either liquid or solid (dust) formulations (99/1, 50/50, and 1/99 liquid/dust ratios). A preliminary review of these data was conducted and the data were considered acceptable for exposure and risk assessment. Study results indicate a maximum transferable residue value of 0.8 mg 3 days post-application from a 4 gram pet medallion. HED typically uses residue transfer data to refine the standard default fraction of application rate transferred (F_{AR}) as described in the Treated Pet SOP. Use of the 0.8 mg residue value results in a F_{AR} value of 0.02% for the 4 gram collar (0.8 mg/4,000 mg = 0.0002, or 0.02%). In absence of submitted data or comments on the form of residues released from the medallion, HED continues to use the range of standard dust to liquid ratios, in conjunction with the F_{AR} input, to estimate exposure, as was done in the residential post-application assessment presented in the DRA.

Table 1 provides a summary of the combined dermal and hand-to-mouth exposure and risk estimates resulting from the pet medallion formulations using the transferable residue value of 0.8 mg. Scenarios resulting in MOEs below the LOC of 300 are considered potential risk estimates of concern. The 99% liquid/1% dust formulation resulted in combined dermal and incidental oral MOEs ranging from 1000 to 1900, which are not of concern for children 1 to < 2 years old. The 50% liquid/50% dust formulation as well as the 1% liquid/99% dust formulations scenarios resulted in MOEs ranging from 35 to 120, which are risk estimates of concern.

Table 1: Revised Residential Post-Application Incidental Oral Exposure Estimates from Zeta Cypermethrin Pet Collar Tag using 99/1, 50/50 and 1/99 Ratios of Liquid/Solid Formulations for children (1-2 yrs.).

Lifestage	Use Site	Route of Exposure	Pet Size	Maximum Application Rate	Liquid Dose (mg/kg/day)	Solid Dose (mg/kg/day)	Combined MOEs[1] (LOC = 300)
99% Liquid/1% Solid							
Child		Dermal & HTM	small	0.0009 lb ai/pet	0.004887	0.20869	1000

Table 1: Revised Residential Post-Application Incidental Oral Exposure Estimates from Zeta Cypermethrin Pet Collar Tag using 99/1, 50/50 and 1/99 Ratios of Liquid/Solid Formulations for children (1-2 yrs.).							
Lifestage	**Use Site**	**Route of Exposure**	**Pet Size**	**Maximum Application Rate**	**Liquid Dose (mg/kg/day)**	**Solid Dose (mg/kg/day)**	**Combined MOEs[1] (LOC = 300)**
	YT-1601 Dog Tag 10% ai Reg. No. 39039-14		medium	0.0013 lb ai/pet	0.003142	0.13416	1600
			large	0.0018 lb ai/pet	0.002666	0.11383	1900
50% Liquid/50% Solid							
Child	**YT-1601 Dog Tag 10% ai Reg. No. 39039-14**	Dermal & HTM	small	0.0009 lb ai/pet	0.0048	0.208	67
			medium	0.0013 lb ai/pet	0.0020	0.134	110
			large	0.0018 lb ai/pet	0.0013	0.113	120
1% Liquid/99% Solid							
Child	**YT-1601 Dog Tag 10% ai Reg. No. 39039-14**	Dermal & HTM	small	0.0009 lb ai/pet	0.00489	0.20869	35
			medium	0.0013 lb ai/pet	0.00314	0.13416	54
			large	0.0018 lb ai/pet	0.00267	0.11383	64

1. Combined MOE = Liquid Dose (mg/kg/day) + Solid Dose (mg/kg/day)

Discussion

Residue transfer: The registrant submission used the transferable residue value as a representation of the entirety of the residue available on the surface of the animal for transfer to the exposed person. The standard FAR value, 2% was used assuming only 2% of the total available residue (0.8 mg) transfers to the exposed person. HED does not support that the maximum residue transfer value represents the entirety of the residue available for transfer on the surface of the animal and instead only that which transferred to the gloved hand. As described previously, this amount (or estimated fraction transferred) is typical of that submitted and used in the calculations instead of the Treated Pet SOP default F_{AR} value as a representation of the fraction of the total residue on the animal which may transfer to the exposed person. The registrant approach would result in an underestimation of residues available and, as a result, the total amount expected to transfer to the exposed person.

Measured Residues: The study author suggests that the maximum residue value of 0.8 mg be multiplied by 3 to estimate transferrable residue values of 2.4, 4.1, and 4.8 mg for small, medium and large dogs respectively. No quantitative rationale was provided for increasing the maximum residue value by 3X. Therefore, HED assumed that the same F_{AR} would be expected for all size collars.

Formulation Type Issue: Y-Tex Corporation's submitted risk assessment assumes that their end-use product is not a dust formulation. Therefore, they presented risk estimates at only the 99%

liquid/1% dust ratio. Furthermore, they maintain that a torsion study is not necessary for their product. HED does not find that the submitted data and/or comments address the dust/liquid formulation issue. Therefore, HED will continue to rely on its existing approach for incorporating chemical-specific transferable residue data in the zeta cypermethrin exposure and risk assessment. HED will also continue to rely on its current approach of assessing the medallion both as a liquid and a solid (99/1, 50/50, and 1/99 liquid/dust). In the absence of submitted data or comments on the form of residues released from the medallion, HED will also continue to recommend submission of a mechanical dust torsion study to provide clarity on the form of residues released from the medallion.

Conclusions

HED has updated the residential post-application exposure and risk assessment for the pet medallion with the submitted residue transfer data, and potential risk estimates of concern remain. HED recommends Y-Tex Corporation submit a torsion study to address the formulation type issue (i.e., liquid vs. dust).

Dust Torsion Study Recommendation

During Registration Review, questions have been raised about the physical forms that are present on the surface of pet collars and on treated pets. Under use conditions, the pet collar active ingredients are removed from the surface of the collar by contact with the dog or cat's hair coat through the activity of the animals. The Agency has been asking registrants to determine the amount of dust present on a collar, or that could be rubbed off of a collar after mechanical stress.

As a demonstration of worst-case conditions that maximize delivery of the active ingredients to the surface of the collar, HED recommends that a study be conducted exposing a pet medallion to mechanical torsion and stress by twisting and pulling the collar multiple times to maximize any potential release of solids from the collar. The torsion of the medallion is meant to exaggerate the typical or expected movement of the tag against the animal to release the active ingredients contained in the medallion matrix. The exaggerated movement is done intentionally to generate what is assumed to be a theoretical maximum amount of dust. The collar may be twisted multiple times at 180° angles to generate the powder or dust on the surface. The concentration of active ingredient in the resulting powder should also be considered.

Proposed steps[1]:

- Prior to the first torsion cycle and after each torsion cycle, the medallion surface and edges are smoothly wiped with a tissue paper.
- Sample of tag is twisted 10 times at 180° angles.
- The total amount of dust/powder generated is then collected and weighed.

[1] These proposed steps are meant as suggested considerations for the registrant to develop a draft torsion study protocol for review. They do not convey or imply an accepted EPA methodology for a torsion study nor is it a complete list of criteria for evaluation.

- The percent of dust (by weight) is provided based on the total weight of the medallion.

As a second option, the registrant could submit information regarding the physical and chemical properties of the end-use product and a description, with supporting data, relating to how the active ingredient formulation is released and activated.

REFERENCES

1. D425964; Cypermethrin, Zeta-cypermethrin, and Alpha-cypermethrin. Draft Human Health Risk Assessment for Registration Review; M. Collantes, 12/21/2017
2. D447429; Cypermethrin(s). HED Response to Public Comments on the Cypermethrin, Zeta-cypermethrin, and Alpha-cypermethrin Draft Risk Assessment for Registration Review; M. Collantes; 3/13/2019.
3. D436833, Tetrachlorvinphos (TCVP) Risk Assessment; W. Britton, 12/21/2016
4. Ethics Review of "Additional Data in Support of Registration of YT-1601 Dog Tag", M. Arling, 4/30/2019